

09/687,267

Set	Items	Description
S1	926	PRENYL(W) TRANSFERASE
S2	5487	FARNESYLTRANSFERASE
S3	6351	S1 OR S2
S4	3648	S3 (5N) INHIBIT?
S5	112	SCH66336
S6	116	R115777
S7	0	L(W) 778,123
S8	65	BMS (W) 214662
S9	265	FTI (W) 277
S10	6	L778123
S11	535	S5 OR S6 OR S7 OR S8 OR S9 OR S10
S12	25	S11 NOT PY>1993
S13	14	RD (unique items)
S14	200	S4 NOT PY>1993
S15	120	RD (unique items)

15/3,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08077331 93366733 PMID: 8360140

Peptidomimetic inhibitors of Ras farnesylation and function in whole cells.

Garcia AM; Rowell C; Ackermann K; Kowalczyk JJ; Lewis MD

Eisai Research Institute, Andover, Massachusetts 01810.

Journal of biological chemistry (UNITED STATES) Sep 5 1993, 268 (25)
p18415-8, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The ras protooncogene is involved in regulation of cell growth. Mutations that activate the protein result in uncontrolled cell growth. Ras undergoes a series of posttranslational processing events, the first of which, farnesylation, is crucial for the function of the protein. **Inhibitors** of the **farnesyltransferase** enzyme are therefore potential candidates for the development of anticancer drugs. Tetrapeptides have been reported to be good inhibitors of this enzyme in vitro. We have synthesized analogs of the tetrapeptide Cys-Val-Phe-Met by replacement of the amino-terminal amide bonds. One inhibitor, B581, is permeable to the cell membrane. In the cell, it inhibits processing of two farnesylated proteins, H-ras and lamin A, but it does not inhibit processing of a geranylgeranylated protein, Rap 1A. Microinjection of B581 into frog oocytes inhibits maturation induced by activated, farnesylated H-ras but not maturation induced by activated, geranylgeranylated H-ras or by progesterone. These results demonstrate that this peptide mimic inhibits farnesylation selectively in the cell. The inhibition of farnesylation results in inhibition of H-ras function.

15/3,AB/6 (Item 6 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

07158950 93303595 PMID: 8316834

Benzodiazepine peptidomimetics: potent inhibitors of Ras farnesylation in animal cells.

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Science (UNITED STATES) Jun 25 1993, 260 (5116) p1937-42, ISSN 0036-8075 Journal Code: UJ7

Contract/Grant No.: HL 20948, HL, NHLBI

Comment in Science. 1993 Jun 25;260(5116) 1877-8

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Oncogenic Ras proteins transform animal cells to a malignant phenotype only when modified by farnesyl residues attached to cysteines near their carboxyl termini. The farnesyltransferase that catalyzes this reaction recognizes tetrapeptides of the sequence CAAX, where C is cysteine, A is an aliphatic amino acid, and X is a carboxyl-terminal methionine or serine. Replacement of the two aliphatic residues with a benzodiazepine-based mimic of a peptide turn generated potent **inhibitors** of **farnesyltransferase** [50 percent **inhibitory** concentration (IC50) < 1 nM]. Unlike tetrapeptides, the benzodiazepine peptidomimetics enter cells and block attachment of farnesyl to Ras, nuclear lamins, and several other proteins. At micromolar concentrations, these inhibitors restored a normal growth pattern to Ras-transformed cells. The benzodiazepine peptidomimetics may be useful in the design of treatments for tumors in which oncogenic Ras proteins contribute to abnormal growth, such as that of the colon, lung, and pancreas.

15/3,AB/7 (Item 7 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

07158949 93303594 PMID: 8316833

Selective inhibition of ras-dependent transformation by a farnesyltransferase inhibitor .

Kohl NE; Mosser SD; deSolms SJ; Giuliani EA; Pompliano DL; Graham SL; Smith RL; Scolnick EM; Oliff A; Gibbs JB

Department of Cancer Research, Merck Research Laboratories, West Point, PA 19486.

Science (UNITED STATES) Jun 25 1993, 260 (5116) p1934-7, ISSN 0036-8075 Journal Code: UJ7

Comment in Science. 1993 Jun 25;260(5116) 1877-8

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase (FPTase), have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. The tetrapeptide analog L-731,735 is a potent and selective inhibitor of FPTase in vitro. A prodrug of this compound, L-731,734, inhibited Ras processing in cells transformed with v-ras. L-731,734 decreased the ability of v-ras-transformed cells to form colonies in soft agar but had no effect on the efficiency of colony formation of cells transformed by either the v-raf or v-mos oncogenes. The results demonstrate selective inhibition of ras-dependent cell transformation with a synthetic organic inhibitor of FPTase.

15/3,AB/8 (Item 8 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

07088901 94012593 PMID: 8407887

Potent inhibition of human tumor p21ras farnesyltransferase by A1A2-lacking p21ras CA1A2X peptidomimetics.

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Journal of biological chemistry (UNITED STATES) Oct 5 1993, 268 (28) p20695-8, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The ras oncogene product p21ras requires farnesylation and subsequent plasma membrane association for its transforming activity. This key post-translational modification is catalyzed by p21ras farnesyltransferase, which transfers farnesyl from farnesylpyrophosphate to the cysteine of the CA1A2X carboxyl-terminal tetrapeptide of p21ras. In the present report, we describe potent inhibition of p21ras farnesyltransferase by CA1A2X peptidomimetics containing no peptidic amide bonds. We synthesized a series of CA1A2X analogues where the 2 aliphatic amino acids A1 and A2 were replaced by a hydrophobic spacer, 3-aminomethylbenzoic acid (AMBA). The peptidomimetic Cys-AMBA-Met, inhibits p21ras farnesyltransferase from human colon carcinoma (COLO-205) and Burkitt's lymphoma (Daudi) with IC50 values of 60 and 120 nM, respectively. Cys-AMBA-Met is 3-, 8-, and 9-fold (COLO-205) and 2-, 5-, and 7-fold (Daudi) more potent than the corresponding tetrapeptides of p21KB-ras (CVIM), p21N-ras (CVVM), and p21KA-ras (CIIM), respectively. Replacing methionine at the X position with negatively charged glutamate reduces its ability to inhibit the enzyme, whereas positively charged lysine at this position abolishes the inhibitory character of the peptidomimetic. A hydrophobic moiety at the X position, as in Cys-AMBA-Phe, retains potent inhibitory activity. Leucine in the X position of CA1A2X is a post-translational signal for protein geranylgeranylation rather than farnesylation, and, as expected,

Cys-AMBA-Leu does not inhibit the enzyme. Furthermore, CVIM, CVVM, and CIIM are farnesylated by human p21ras farnesyltransferases and inhibit these enzymes by serving as alternative substrates. In contrast, the peptidomimetics described here are true p21ras **farnesyltransferase inhibitors** since none is farnesylated by this enzyme.

15/3,AB/12 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08998572 BIOSIS NO.: 199497006942

Potent inhibition of human tumor p21-ras farnesyltransferase by A-1A-2-lacking p21-ras CA-1A-2X peptidomimetics.

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JOURNAL: Journal of Biological Chemistry 268 (28):p20695-20698 1993

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The ras oncogene product p21-ras requires farnesylation and subsequent plasma membrane association for its transforming activity. This key post-translational modification is catalyzed by p21-ras farnesyltransferase, which transfers farnesyl from farnesylpyrophosphate to the cysteine of the CA-1A-2X carboxyl-terminal tetrapeptide of p21-ras. In the present report, we describe potent **inhibition** of p21-ras **farnesyltransferase** by CA-1A-2X peptidomimetics containing no peptidic amide bonds. We synthesized a series of CA-1A-2X analogues where the 2 aliphatic amino acids A-1 and A-2 were replaced by a hydrophobic spacer, 3-aminomethylbenzoic acid (AMBA). The peptidomimetic Cys-AMBA-Met, **inhibits** p21-ras **farnesyltransferase** from human colon carcinoma (COLO-205) and Burkitt's lymphoma (Daudi) with IC-50 values of 60 and 120 nM, respectively. Cys-AMBA-Met is 3-, 8-, and 9-fold (COLO-205) and 2-, 5-, and 7-fold (Daudi) more potent than the corresponding tetrapeptides of p21-K1B-ras (CVIM), p21-N-ras (CVVM), and P21-K1A-ras (CIIM), respectively. Replacing methionine at the X position with negatively charged glutamate reduces its ability to inhibit the enzyme, whereas positively charged lysine at this position abolishes the inhibitory character of the peptidomimetic. A hydrophobic moiety at the X position, as in Cys-AMBA-Phe, retains potent inhibitory activity. Leucine in the X position of CA-1A-2X is a post-translational signal for protein geranylgeranylation rather than farnesylation, and, as expected, Cys-AMBA-Leu does not inhibit the enzyme. Furthermore, CVIM, CVVM, and CIIM are farnesylated by human p21-ras farnesyltransferases and inhibit these enzymes by serving as alternative substrates. In contrast, the peptidomimetics described here are true p21-ras **farnesyltransferase inhibitors** since none is farnesylated by this enzyme.

1993

15/3,AB/13 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08640928 BIOSIS NO.: 199345059003

UCF1, protein farnesyltransferase inhibitors from Streptomyces: Antitumor activity in murine tumors models with activated ras.

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JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 34 (0):p386 1993
CONFERENCE/MEETING: 84th Annual Meeting of the American Association for Cancer Research Orlando, Florida, USA May 19-22, 1993
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1993

15/3,AB/23 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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05524144 EMBASE No: 1993292243
Potent inhibition of human tumor p21(ras) farnesyltransferase by Ainf 1Ainf 2- lacking p21(ras) CAinf 1Ainf 2X peptidomimetics
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Department of Pharmacology, Faculty of Arts and Sciences, University of Pittsburgh, Pittsburgh, PA 15261 United States
Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1993 , 268/28 (20695-20698)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The ras oncogene product p21(ras) requires farnesylation and subsequent plasma membrane association for its transforming activity. This key post-translational modification is catalyzed by p21(ras) farnesyltransferase, which transfers farnesyl from farnesylpyrophosphate to the cysteine of the CAinf 1Ainf 2X carboxyl-terminal tetrapeptide of p21(ras). In the present report, we describe potent **inhibition of p21(ras) farnesyltransferase** by CAinf 1Ainf 2X peptidomimetics containing no peptidic amide bonds. We synthesized a series of CAinf 1Ainf 2X analogues where the 2 aliphatic amino acids Ainf 1 and Ainf 2 were replaced by a hydrophobic spacer, 3-aminomethylbenzoic acid (AMBA). The peptidomimetic Cys-AMBA-Met, **inhibits p21(ras) farnesyltransferase** from human colon carcinoma (COLO-205) and Burkitt's lymphoma (Daudi) with IC₅₀ values of 60 and 120 nM, respectively. Cys-AMBA-Met is 3-, 8-, and 9-fold (COLO-205) and 2-, 5-, and 7-fold (Daudi) more potent than the corresponding tetrapeptides of p21(K(B)-ras) (CVIM), p21(N-ras) (CVVM), and p21(K(A)-ras) (CIIM), respectively. Replacing methionine at the X position with negatively charged glutamate reduces its ability to inhibit the enzyme, whereas positively charged lysine at this position abolishes the inhibitory character of the peptidomimetic. A hydrophobic moiety at the X position, as in Cys-AMBA-Phe, retains potent inhibitory activity. Leucine in the X position of CAinf 1Ainf 2X is a post-translational signal for protein geranylgeranylation rather than farnesylation, and, as expected, Cys-AMBA-Leu does not inhibit the enzyme. Furthermore, CVIM, CVVM, and CIIM are farnesylated by human p21(ras) farnesyltransferases and inhibit these enzymes by serving as alternative substrates. In contrast, the peptidomimetics described here are true p21(ras) **farnesyltransferase inhibitors** since none is farnesylated by this enzyme.

15/3,AB/25 (Item 1 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text
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02531913 H.W. WILSON RECORD NUMBER: BGS193031913
Novel anticancer agents move closer to reality.
AUGMENTED TITLE: **farnesyltransferase inhibitors**
Travis, John
Science (Science) v. 260 (June 25 '93) p. 1877-8
SPECIAL FEATURES: il ISSN: 0036-8075
LANGUAGE: English

COUNTRY OF PUBLICATION: United States

ABSTRACT: New and better cancer therapies may result from research on drugs that can prevent mutated ras genes from making cells cancerous. Ras is an oncogene responsible for 20 percent of all known forms of cancer, most notably colon cancer. Proteins encoded by ras genes are responsible for helping cells respond to growth factors. When mutated, the ras genes are "turned on" and promote runaway cell division, causing the spread of cancer. Two independent research teams, one from Merck Research Laboratories and the other from Genentech and the University of Texas Southwestern Medical Center, have discovered ras-controlling compounds. The compounds, which disrupt a reaction catalyzed by the enzyme farnesyltransferase, target the earliest step in the maturation of the protein generated by ras. .

15/3,AB/32 (Item 7 from file: 144)

DIALOG(R) File 144:Pascal

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10967146 PASCAL No.: 93-0476612

Selective inhibition of farnesyl-protein transferase blocks ras processing in vivo

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Journal: The Journal of biological chemistry, 1993, 268 (11) 7617-7620

Language: English

The ras oncogene product, Ras, is synthesized in vivo as a precursor protein that requires post-translational processing to become biologically active and to be capable of transforming mammalian cells. Farnesylation appears to be a critical modification of Ras, and thus inhibitors of the farnesyl-protein transferase (FPTase) that catalyzes this reaction may block ras-dependent tumorigenesis. Three structural classes of FPTase inhibitors were identified: (alpha -hydroxyfarnesyl)phosphonic acid, chaetomelic acids, and zaragozic acids. By comparison, these compounds were weaker inhibitors of geranylgeranyl-protein transferases. Each of these inhibitors was competitive with respect to farnesyl diphosphate in the FPTase reaction

15/3,AB/53 (Item 9 from file: 266)

DIALOG(R) File 266:FEDRIP

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00306482

IDENTIFYING NO.: 1R21CA91518-01 AGENCY CODE: CRISP

Farnesyltransferase Inhibitor **Therapy for Myelodysplasia**

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PERFORMING ORG.: UNIVERSITY OF TEXAS MD ANDERSON CAN CTR, HOUSTON, TEXAS

SPONSORING ORG.: NATIONAL CANCER INSTITUTE

FY : 2001

SUMMARY: DESCRIPTION (Provided by applicant): Patients with myelodysplastic syndrome (MDS) suffer from, and often succumb to, serious infections or bleeding because of severe pancytopenia, with or without progression to acute leukemia. Current therapy for MDS does not yield a survival advantage, and no form of therapy has proven advantageous enough to warrant being considered standard. Mutated RAS genes are found in about 20 percent-30 percent of patients with MDS. Furthermore, in patients without RAS mutations, Ras may still be activated indirectly because of the effects of other genetic aberrations. It is now known that in order for even mutated Ras to be active, it must move from the cytoplasm to the plasma membrane, a process in which the addition of a farnesyl group by the farnesyltransferase enzyme (FTase) plays an important role. Recently, novel

compounds which act as FTase inhibitors and hence interfere with Ras activation have been developed. The goal of this project will be to perform the first clinical study of a novel FTase inhibitor (R115777) in MDS patients and to ascertain the optimum dose for biologic and clinical response. (R115777 is available from the Cancer Therapy and Evaluation Program of the National Cancer Institute.) Our hypothesis is that the patients most likely to respond are those who have baseline Ras activation which can be downregulated after treatment with an FTase inhibitor. We will start with a Phase I dose-finding study. The objective of the initial trial will be to ascertain patient tolerance to R115777, and to estimate optimum biologic dose. These trials will then be expanded to determine subsets of patients who are most likely to show biologic and clinical response. The optimum dose and subsets of patients with biologic response to R115777 will be ascertained by measuring the relationship between administered dose and plasma concentration of R115777 and effects on biologic endpoints: FTase activity, Ras and lamin B farnesylation, and downstream effectors of Ras (MAP kinase and IL-1 (the latter based on our recent results demonstrating that Ras activation leads to autocrine IL-1 production in leukemia)). In summary, this work will determine a dose of R115777 which is both tolerable and maximizes the impact of this molecule on the FTase/Ras system. This dose will then be used to determine if R115777 is effective in the treatment of MDS and if certain molecular/biologic markers are predictive of response. These studies will also enhance our understanding of the relationship between inhibition of farnesylation, effects on downstream effectors, and antitumor activity in MDS, and should be useful as a paradigm for the clinical application of other FTase inhibitors.

15/3,AB/54 (Item 10 from file: 266)
DIALOG(R) File 266:FEDRIP
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00306115

IDENTIFYING NO.: 1R01CA90321-01 AGENCY CODE: CRISP
TREATMENT OF BCR/ABL CAUSED LEUKEMIAS WITH FTIs
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PERFORMING ORG.: CHILDREN'S HOSPITAL LOS ANGELES, LOS ANGELES, CALIFORNIA
SPONSORING ORG.: NATIONAL CANCER INSTITUTE
FY : 2001

SUMMARY: DESCRIPTION: The Bcr/Abl oncoprotein causes the development of Ph-chromosome-positive leukemias. Bcr/Abl P210 and P190 share a domain of Abi which encodes a deregulated tyrosine kinase. This activity perturbs a number of downstream signal transduction pathways including that of the small GTPase Ras. **Inhibitors** of the enzyme **farnesyltransferase** (FTIs) have been tested as possible therapeutic agents against Ras-associated solid tumors in man. We have generated a transgenic mouse model which clinically mimics Ph-positive acute lymphoblastic leukemia and tested the potential therapeutic properties of an FTI in this model. Our data show that FTIs are surprisingly potent in preventing the emergence of overt leukemia in our mice. We therefore hypothesize that FTIs are effective in the treatment of Bcr/AbI caused leukemias by interfering with specific small GTPases necessary for disease progression. We will explore this by determining which cellular characteristics known to be altered by Bcr/AbI expression including apoptosis, cytokine independence, mitogenesis and adhesion are affected by the FTIs in BaF3 lymphoid cells with regulatable Bcr/Abl expression. It will also be investigated which small GTPases including Ras are activated by Bcr/Abl in cell line and animal models, and which are targeted by treatment with the FTIs. In addition, we will evaluate whether the FTIs are effective against terminal-stage disease in the Bcr/AbI P190 transgenic mouse model, whether they can cure P190-caused leukemia/lymphoma in a bone marrow transplant model and whether Bcr/Abl-expressing cells develop resistance to FTIs. By utilizing a compound which apparently acts on downstream targets of Bcr/Abl in vivo, these experiments will provide unique insights into the mechanisms by which

February 21, 2002

Bcr/Abl causes leukemia. These studies will also help pinpoint which pathway(s) are critical in transducing the oncogenic signals of Bcr/Abl, which could provide additional targets for therapeutic intervention. Finally, data will emerge which will be invaluable in the assessment of Using FTIs in the treatment of Ph-positive leukemia in man

15/3,AB/55 (Item 11 from file: 266)

DIALOG(R) File 266:FEDRIP

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00304798

IDENTIFYING NO.: 1R01CA85709-01A1 AGENCY CODE: CRISP

AKT SURVIVAL PATHWAYS AND FARNESYLTRANSFERASE INHIBITOR INDUCED APOPTOSIS

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SPONSORING ORG.: NATIONAL CANCER INSTITUTE

FY : 2001

SUMMARY: FTIs have been shown to inhibit the growth of human tumors in preclinical animal models and are presently in clinical trials but their mechanism of antitumor activity is unknown. The hypothesis upon which this proposal is based is that FTIs inhibit tumor growth by inducing apoptosis through inhibition of phosphatidyl inositol-3-kinase (PI3K)/AKT-mediated survival and adhesion pathways. This hypothesis will be tested through the following specific aims: 1) To determine the involvement of the AKT survival pathway in FTI-277-induced apoptosis; 2) To determine the ability of FTI-277 to disrupt PI3-kinase/AKT mediated cell survival and adhesion pathways; 3) To determine the involvement of H-ras, N-ras and K-ras in mediating activation of the PI3K/AKT survival pathways, and their implication in FTI-277-induced apoptosis, and; 4) To determine the involvement of the AKT survival pathway in FTI-277 antitumor activity in the nude mouse human tumor xenograft model. Two highly potent and selective but structurally unrelated FTIs (L-739,750 and SCH66336) will be used to confirm these findings.

15/3,AB/56 (Item 12 from file: 266)

DIALOG(R) File 266:FEDRIP

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00303740

IDENTIFYING NO.: 5R01CA82222-03 AGENCY CODE: CRISP

ROLE OF RHO IN FARNESYLTRANSFERASE INHIBITOR RESPONSES

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SPONSORING ORG.: NATIONAL CANCER INSTITUTE

FY : 2001

SUMMARY: **Farnesyltransferase inhibitors** (FTIs) are among the first 'designer drugs' in clinical trials aimed at blocking cancer cell signal transduction. FTIs were made to attack tumors containing oncogenic Ras, whose function depends upon posttranslational farnesylation. Preclinical trials have demonstrated strikingly specific effects of FTIs against malignantly transformed cells. However, mechanistic investigations have raised doubts that Ras is a necessary target for drug inhibition. Thus, the mechanism of action and identity of FTI target proteins other than Ras have emerged as important questions. Guiding Hypothesis and Specific Aims. We propose to test the hypothesis that FTIs act in part through alteration of Rho prenylation and function (the 'FTI-Rho hypothesis'). Preliminary studies prompt RhoB as a paradigm for study. Cell adhesion and gene activation events related to FTI response and Rho alteration will be investigated. Mechanisms that distinguish apoptosis and cell growth inhibition by FTIs will be defined. In short, we aim to 1) establish Rho as an FTI target, 2) identify Rho-dependent events required to mediate FTI

response, and 3) define the factors that dictate growth inhibition versus apoptosis. Innovation and Significance. The main element of innovation in our proposal is the shift of intellectual focus from Ras to Rho as a realm to understand the mechanism of FTI action in cancer cells. Defining FTI mechanism(s) will promote clinical applications as well as novel insights in to cancer cell pathophysiology.

15/3,AB/58 (Item 14 from file: 266)

DIALOG(R)File 266:FEDRIP

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00301892

IDENTIFYING NO.: 2R01CA75248-05A1 AGENCY CODE: CRISP

Acyltransferase Inhibitors as Anti Ras Agents

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PERFORMING ORG.: PENNSYLVANIA STATE UNIV HERSHEY MED CTR, HERSHEY, PENNSYLVANIA

SPONSORING ORG.: NATIONAL CANCER INSTITUTE

FY : 2001

SUMMARY: DESCRIPTION: Mutational activation of ras oncogene products (p21 s) is involved in the loss of growth control in a high percentage of human tumors. Consequently, significant attention has focused on defining the biochemistry and pharmacology of p21s, with the ultimate goal of developing inhibitors of p21 to be used as antitumor drugs. P21 S require extensive post-translational processing to express optimal transforming ability, including attachment of farnesyl and palmitoyl moieties to cysteine residues near the C-terminus. While several inhibitors of farnesyltransferase inhibitors have been described; the biochemistry and pharmacology of the palmitoylation step have not yet elucidated.

During the initial funding period of this grant, we demonstrated that a natural product called cerulenin inhibits protein palmitoylation and inhibits the signaling activities of p21. Furthermore, we synthesized a series of alkyloxiranecarboxamides, including certain radiolabeled compounds, as cerulenin analogs, and some of these compounds were shown to be selective inhibitors of protein palmitoylation. This was the first demonstration of selective inhibitors of this molecular target. Analysis of protein alkylation by the radiolabeled compounds has identified a few candidate proteins for the heretofore unpurified human p21 acyltransferase (PATase) that palmitoylates Ras proteins. We are currently in a unique position to characterize this enzyme both biochemically and pharmacologically.

In studies to be conducted under this Continuation, we will: 1) continue the isolation and biochemical characterization of human PATase; 2) design and synthesize additional inhibitors of PATase; 3) evaluate the anti-tumor potential of PATase inhibitors in vivo; and 4) further assess the biological consequences of inhibiting PATase in vitro. These efforts are logical and feasible extensions of work completed during the initial funding period. Overall, they should allow critical evaluation of PATase as a target for new anticancer drugs.

15/3,AB/59 (Item 15 from file: 266)

DIALOG(R)File 266:FEDRIP

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00301584

IDENTIFYING NO.: 5R01CA73820-04 AGENCY CODE: CRISP

TUMOR RADIOSENSITIZATION BY PRENYLTRANSFERASE INHIBITORS

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SPONSORING ORG.: NATIONAL CANCER INSTITUTE

FY : 2001

SUMMARY: DESCRIPTION: One obstacle to successful radiotherapy is the elevated resistance to ionizing radiation that many tumors display relative to adjacent normal tissues. Thus the radiosensitivity of normal tissue limits the radiation dose that can be delivered to a tumor. The combined effect of tumor resistance and normal tissue sensitivity can result in incomplete elimination of tumor cells and local recurrence. This grant address this problem by developing a method to specifically sensitize tumor cells to radiation using an approach based on the contribution of ras oncogenes to radiation resistance. Ras oncogenes are frequently mutated in human tumors treated with radiation therapy. These include pancreatic, colon, ovarian, and thyroid carcinomas sarcomas and late stage cervical carcinomas. Ras mutations have furthermore been shown to cause increase radiation resistance in experimental tumor systems. Thus, inhibition of the activity of oncogenic ras might be hypothesized to lead to radiation sensitization of the tumor cells. Since normal cells do not contain oncogenic ras, such an approach should not affect these cells.

Farnesyltransferase and geranylgeranyltransferase **inhibitors** are compounds that specifically inhibit the post-translational prenylation of ras which is required for membrane association and signal transduction activity. The action of **farnesyltransferase inhibitors** (FTI) appears to be greatest against activated H-ras oncogenes, and consequently little or no effect is seen in normal cells as doses that significantly alter the morphology, growth and radiation-resistance of H-ras transformed cells. Geranylgeranyltransferase inhibitors (GGTI) show selective activity against K-ras prenylation. Both inhibitors have been shown to impede tumor growth, and are thus ideal candidates for combined modality therapy with radiation. The goal of this study is to determine whether the specificity of these inhibitors for the activated ras in tumor cells can be exploited such that these agents can be used as tumor cell radiosensitizers during radiation therapy.

15/3,AB/60 (Item 16 from file: 266)

DIALOG(R) File 266:FEDRIP

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00300752

IDENTIFYING NO.: 5U19CA67771-07 0003 AGENCY CODE: CRISP

ADAPTIVE IMMUNOTHERAPY--LONG CIRCULATING MACROMOLECULAR THERAPEUTICS

PRINCIPAL INVESTIGATOR: DER, CHANNING J

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PERFORMING ORG.: UNIVERSITY OF SOUTH FLORIDA, TAMPA, FLORIDA

SPONSORING ORG.: NATIONAL CANCER INSTITUTE

FY : 2001

SUMMARY: Description: (Applicant's Description) Our previous NCDDG assessed and developed **farnesyltransferase inhibitors** (FTIs) as anti-Ras drugs. From those studies arose an appreciation that inhibitors of protein geranylgeranyltransferase I (GGTIs) may also be useful as anti-Ras and anti-cancer drugs. The overall long-term goal of this NCDDG is to develop GGTIs as novel anti-cancer drugs. Three key observations link geranylgeranylated (GG) pro FTI-treated K-Ras and N-Ras proteins become alternatively prenylated by GG and escape the inhibitory action of FTIs. Second, the Ras-related proteins R-Ras and R-Ras2/TC21 are GG-modified and their aberrant activation can promote tumorigenic transformation and tumor cell invasion. Third, members of the Rho family of Ras GG-modified, are required for the transforming actions of Ras and other oncoproteins, and their aberrant activation can cause tumor cell invasion and metastasis. Finally, recent work from this NCDDG showed that GGTIs can arrest human tumor cell growth in vitro and reduce tumorigenicity in vivo. Taken together, these observations support the importance of targeting the function of GG-modified proteins for cancer treatment. The two broad goals of Program #3 of this NCDDG are (a) to determine if specific GG-modified members of the Ras superfamily of proteins are targets of GGTIs, and (b) to identify genes whose expression are regulated by geranylgeranylated

proteins and are therefore the targets of GGTI-mediated growth inhibition. Three specific aims are proposed: (1) to determine if R-Ras and TC21 are targets for GGTI-mediated growth inhibition, (2) to determine if Rac1, RhoA, and Cdc42 are targets for GGTI-mediated growth inhibition, and (3) to identify genes whose expression are altered by GGTI-mediated inhibition of geranylgeranylation and cellular proliferation. The GGTIs in Program #1 will be essential for our studies and the in vitro and in vivo analyses of GGTI activity proposed for Program #2 will strongly complement our analysis.

15/3,AB/61 (Item 17 from file: 266)
DIALOG(R) File 266:FEDRIP
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00300511

IDENTIFYING NO.: 5R01CA64514-09 AGENCY CODE: CRISP
CANCER CHEMOPREVENTION BY SILYMARIN
PRINCIPAL INVESTIGATOR: AGARWAL, RAJESH
ADDRESS: UNIVERSITY OF COLORADO HLTH SC 4200 EAST 9TH AVE DENVER,
COLORADO 80262
PERFORMING ORG.: UNIVERSITY OF COLORADO HLTH SCIENCES CTR, DENVER,
COLORADO
SPONSORING ORG.: NATIONAL CANCER INSTITUTE
FY : 2001

SUMMARY: In recent years, considerable emphasis is placed on identifying new cancer chemopreventive agents which could be useful for human population. In this regard, the identification of better anti-tumor promoting agents is highly desired since these agents appear to have greater relevance in preventing against the development of neoplasms. Silymarin, an antioxidant flavonoid isolated from artichoke, has been shown to possess significant protective effects against hepatotoxicity and other disorders. Studies employing cell or organ culture systems have suggested that silymarin may possess anti-tumor promoting effects. In a recent study, we observed that silymarin significantly inhibits 12-O-tetradecanoylphorbol-13-acetate (TPA)- and other skin tumor promoter-induced epidermal ornithine decarboxylase (ODC) activity, and TPA-induced epidermal ODC mRNA expression. Primary studies also showed that topical application of silymarin prior to that of TPA affords significant protection against tumor promotion in terms of both tumor incidence and tumor multiplicity in SENCAR mouse skin. Together, these studies strengthen the possibility that silymarin could be a significantly useful anti-tumor promoting agent. Our preliminary data also show that in cell culture system silymarin inhibits farnesyltransferase (FTase) activity concomitant with the decrease in Ha-ras p21 membrane localization, and was not inhibitory to 3-hydroxy-3-methylglutaryl coenzyme A reductase. Silymarin also showed selective inhibition of the growth of vHa-ras oncogene transformed NIH3T3 cells compared to normal NIH3T3 cells. Collectively, cell culture studies suggested that silymarin selectively inhibits FTase and thereby ras p21 farnesylation leading to a significant decrease in the growth of activated ras oncogene carrying cells. In this proposal, we will extend these studies to evaluate in detail the anti-tumor promoting effects of silymarin at cellular, biochemical, and molecular levels. Studies will be performed to assess: i) the dose-dependent protective effect of topical application of silymarin against TPA- and okadaic acid-caused skin tumor promotion in SENCAR mice; ii) the inhibitory effect of silymarin against the cellular, biochemical and molecular changes associated with tumor promotion; iii) whether silymarin is a stage specific inhibitor of tumor promotion; and iv) the inhibitory effect of silymarin on FTase mRNA expression, FTase activity and Ha-ras p21 membrane localization during murine skin tumorigenesis. Studies will also be performed to assess the selectivity of silymarin in inhibiting FTase mRNA expression, FTase activity, Ha-ras p21 membrane localization and cell growth employing SP-1 (carry activated Ha-ras oncogene) and PA (not carry activated Ha-ras oncogene) cell lines derived from DMBA- TPA induced papillomas in SENCAR mouse skin. The results of the proposed studies will identify a new agent with significant anti-tumor promoting effect, and will define in particular

the Ha-ras mediated mechanism of such protective effect.

15/3,AB/64 (Item 1 from file: 315)
DIALOG(R)File 315:ChemEng & Biotec Abs
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326534 CEABA Accession No.: 24-12-019137 DOCUMENT TYPE: Journal
Title: Anticancer compounds revealed
CORPORATE SOURCE: Merck Sharpe Dohme USA Genentech Inc. USA Eisai Co.
Ltd. USA
JOURNAL: BIOTECHNOLOGY BUSINESS NEWS, Volume: 3, Issue: 60, Page(s): 15
CODEN: QQQQQQ
PUBLICATION DATE: 16 Jul 1993 (930716) LANGUAGE: English
ABSTRACT: Three research teams working independently of each other have
come up with new anticancer compounds that function at a biochemical
level. Each is able to block mutated ras genes to make cells cancerous.
The ras oncogene is believed to be linked to at least a fifth of all
human cancers and over a half of colon and pancreatic carcinomas. Merck
has synthesized a tetrapeptide that **inhibits farnesyltransferase**,
thus blocking the ability of ras to transform cells into carcinomas.

15/3,AB/73 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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119197835 CA: 119(19)197835f JOURNAL
Protein prenylation: key to ras function and cancer intervention?
AUTHOR(S): Khosravi-Far, Roya; Cox, Adrienne D.; Kato, Kiyoko; Der,
Channing J.
LOCATION: La Jolla Cancer Res. Found., La Jolla, CA, 92037, USA
JOURNAL: Cell Growth Differ. DATE: 1992 VOLUME: 3 NUMBER: 7 PAGES:
461-9 CODEN: CGDIE7 ISSN: 1044-9523 LANGUAGE: English

15/3,AB/74 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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119181244 CA: 119(17)181244b PATENT
**Preparation of reduced peptides as inhibitors of farnesyl protein
transferase**
INVENTOR(AUTHOR): Graham, Samuel L.; Desolms, S. Jane; Garsky, Victor M.
LOCATION: USA
ASSIGNEE: Merck and Co., Inc.
PATENT: European Pat. Appl. ; EP 535731 A2 DATE: 930407
APPLICATION: EP 92202924 (920923) *US 770078 (910930)
PAGES: 16 pp. CODEN: EPXXDW LANGUAGE: English CLASS: C07K-005/08A;
C07K-005/02B; C07K-005/06B; A61K-037/64B DESIGNATED COUNTRIES: CH; DE; FR;
GB; IT; LI; NL

15/3,AB/75 (Item 7 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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119180386 CA: 119(17)180386n PATENT
**Preparation of itaconate and mesaconate analogs as inhibitors of farnesyl
protein transferase**
INVENTOR(AUTHOR): Singh, Sheo Bux
LOCATION: USA
ASSIGNEE: Merck and Co., Inc.
PATENT: European Pat. Appl. ; EP 547672 A2 DATE: 930623
APPLICATION: EP 92203809 (921208) *US 809199 (911216)
PAGES: 12 pp. CODEN: EPXXDW LANGUAGE: English CLASS: C07C-057/13A;

A61K-031/19B; C07C-211/00B DESIGNATED COUNTRIES: CH; DE; FR; GB; IT; LI; NL

15/3,AB/76 (Item 8 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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119160836 CA: 119(15)160836f PATENT
Preparation of petptide analogs as inhibitors of farnesyl protein transferase
INVENTOR(AUTHOR): Graham, Samuel L.; Desolms, S. Jane
LOCATION: USA
ASSIGNEE: Merck and Co., Inc.
PATENT: European Pat. Appl. ; EP 535730 A2 DATE: 930407
APPLICATION: EP 92202923 (920923) *US 768798 (910930)
PAGES: 15 pp. CODEN: EPXXDW LANGUAGE: English CLASS: C07K-005/08A;
C07K-005/06B; A61K-037/64B DESIGNATED COUNTRIES: CH; DE; FR; GB; IT; LI; NL

15/3,AB/78 (Item 10 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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119131512 CA: 119(13)131512s PATENT
Inhibitors of farnesyl protein transferase as anticancer agents
INVENTOR(AUTHOR): Dufresne, Claude; Vanmiddlesworth, Frank L.; Wilson, Kenneth E.
LOCATION: USA
ASSIGNEE: Merck and Co., Inc.
PATENT: Britain UK Pat. Appl. ; GB 2261375 A1 DATE: 930519
APPLICATION: GB 9223250 (921106) *US 793055 (911115)
PAGES: 45 pp. CODEN: BAXXDU LANGUAGE: English CLASS: A61K-031/34A

15/3,AB/80 (Item 12 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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119108490 CA: 119(11)108490z JOURNAL
Farnesyl transferase as a target for non-cytotoxic anticancer agents: First steps
AUTHOR(S): Tassin, Jean Pierre; Boutin, Jean A.; Ernould, Anne Pascale; Atassi, Ghanem
LOCATION: Div. Cancerol. Exp., Inst. Rech. Serv., 92150, Suresnes, Fr.
JOURNAL: C. R. Seances Soc. Biol. Ses Fil. DATE: 1991 VOLUME: 185
NUMBER: 5 PAGES: 306-11 CODEN: CRSBAW ISSN: 0037-9026 LANGUAGE: French

15/3,AB/99 (Item 3 from file: 77)
DIALOG(R)File 77:Conference Papers Index
(c) 2002 Cambridge Sci Abs. All rts. reserv.

4568978
Supplier Accession Number: 01-02413 V29N02
Re-oxygenation of tumors expressing activated H-ras after farnesyltransferase inhibitor L744, 832 treatment
Cohen-Jonathan, E.L.; Cerniglia, G.; Evans, S.M.; Koch, C.J.; Muschel, R.J.; McKenna, W.G.; Gibbs, J.B.; Thompson, T.C.; Bernhard, E.J.
Institut Claudius Regaud, Toulouse, France
Annual Meeting of the American Society of Therapeutic Oncology 0040023
Boston, Massachusettes (USA) 22-26 Oct 2000
American Society for Therapeutic Oncology
International Journals Biology Physics, ; phone: (212) 633-3730/1; fax:

15/3,AB/101 (Item 5 from file: 77)
DIALOG(R)File 77:Conference Papers Index
(c) 2002 Cambridge Sci Abs. All rts. reserv.

4519937
Supplier Accession Number: 00-04454 V28N04
Farnesyltransferase inhibitors: From peptidomimetics to the clinical agent BMS-214662
Hunt, J.T.; Manne, V.
219. Meeting and Exposition of the American Chemical Society 0010107
San Francisco, CA (USA) 26-30 Mar 2000
American Chemical Society
American Chemical Society, 1155 16th St., NW, Washington, DC 20036, USA;
phone: (202) 872-6059; fax: (202) 872-6128; email: v.beatty@acs.org; URL:
www.acs.org

15/3,AB/102 (Item 6 from file: 77)
DIALOG(R)File 77:Conference Papers Index
(c) 2002 Cambridge Sci Abs. All rts. reserv.

4519931
Supplier Accession Number: 00-04454 V28N04
Farnesyltransferase inhibitors as potential anticancer agents
Gibbs, J.B.; Anthony, N.J.; Buser, C.A.; DeSolms, S.J.; Graham, S.L.;
Hartman, G.D.; Heimbroke, D.C.; Lobell, R.B.; Koblan, K.S.; Kohl, N.E.
219. Meeting and Exposition of the American Chemical Society 0010107
San Francisco, CA (USA) 26-30 Mar 2000
American Chemical Society
American Chemical Society, 1155 16th St., NW, Washington, DC 20036, USA;
phone: (202) 872-6059; fax: (202) 872-6128; email: v.beatty@acs.org; URL:
www.acs.org

15/3,AB/104 (Item 8 from file: 77)
DIALOG(R)File 77:Conference Papers Index
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4396072
Supplier Accession Number: 98-06875 V26N06
Effect of the peptidomimetic farnesyltransferase inhibitors PD 152440 and PD 169451 on protein prenylation and rat smooth muscle cell proliferation
Arnaboldi, L.; Sebolt-Leopold, J.; Paoletti, R.; Fumagalli, R.; Corsini, A.
Inst. Pharmacological Sci., Milan
8th International Symposium on Drugs Affecting Lipid Metabolism
9825028 Florence (Italy) 30 May - 3 Jun 1998
Giovanni Lorenzini Medical Foundation, Cornell University Medical College, Fondazione Italiana per Il Cuore
DALM '98, 6565 Fannin Street, MS A-601, Houston, TX 77030, USA; phone: (713) 797-0401; fax: (713) 796-8853; email: ajacksoncm.tmc.edu, Abstracts available. Contact Giovanni Lorenzini Medical Foundation for price.

15/3,AB/108 (Item 12 from file: 77)
DIALOG(R)File 77:Conference Papers Index
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4310101
Supplier Accession Number: 97-05508 V25N05
"Farnesyltransferase inhibitors and anti-ras therapy"
Gibbs, J.B.

38th Annual Meeting of the British Association for Cancer Research
9720576 Southampton (UK) 1-4 Apr 1997
British Association for Cancer Research
Churhill Livingstone, Robert Stevenson House, 1-3 Baxter's Place, Leith
Walk, Edinburgh EH1 3AF, UK, Abstracts available.
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